PCT

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FORM PTO-1390 (REV. 9-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

GEI-061

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5): 09/051246

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR97/01452	August 5, 1997	August 5, 1996

TITLE OF INVENTION: NOVEL STABLE PARACETAMOL-BASED LIQUID FORMULATIONS AND A METHOD FOR PREPARING THE SAME

APPLICANT(S) FOR DO/EO/US: DIETLIN et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau)
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (Unexecuted)
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
	PCT/FR97/01452	GEI-061

17		CALCULATIONS	PTO USE ONLY
☒	The following fees are submitted.		
	Basic National Fee (37 CFR 1.492(a)(1)-(5)):	$1070.00	
	Search Report has been prepared by the EPO or JPO ... $830.00		
	International preliminary examination fee paid to USPTO (37 CFR 1.482) ... $640.00		
	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ... $710.00		
	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO ... $950.00		
	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ... $90.00		
	ENTER APPROPRIATE BASIC FEE AMOUNT =	$1070.00	
	Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	27 -20 =	7	X $22.00	$ 154.00	
Independent Claims	1 -3 =	0	X $74.00	$	
Multiple dependent claims(s) (if applicable)			+ $230.00	$ 1224.00	
TOTAL OF ABOVE CALCULATIONS =				$	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1224.00	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
TOTAL NATIONAL FEE =				$ 1224.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 1224.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 1224.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Form PTO-1390 (REV 5-93)

Our Ref.: GEI-061

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
PCT/FR97/01452 : PCT Date: August 5, 1997
DIETLIN et al
Serial No.:
Filed: Concurrently Herewith
For: NOVEL STABLE PARACETAMOL-BASED LIQUID FORMULATIONS AND A METHOD FOR PREPARING THE SAME

600 Third Avenue
New York, NY 10016
April 3, 1998

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE CLAIMS:

Claim 3, line 2, cancel "and claim 2".

Claim 4, line 2, cancel "anyone of claims 1 to 3" and insert --claim 1--.

Claim 5, line 2, cancel "anyone of claims 1 to 4" and insert --claim 1--.

Claim 6, line 2, cancel "anyone of claims 1 to 4" and insert --claim 1--.

Claim 8, line 2, cancel "or claim 7".

Claim 10, line 2, cancel "and claim 9".

Claim 11, line 2, cancel "and claim 7".

Claim 12, line 2, cancel "and 7".

Claim 14, line 2, cancel "anyone of claims 1 to 13" and insert --claim 1--.

Claims 15 to 19, line 2 of each, cancel "anyone of claims 1 to 14" and insert --claim 1--.

Claims 22 and 24 to 26, line 2 of each, cancel "anyone of claims 1 to 14" and insert --claim 1--.

Claim 27, line 2, cancel "anyone of claims 1 to 11" and insert --claim 1--.

REMARKS

The amendment is being filed in order to remove improperly

dependent claims from the application.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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CAM:sd
Enclosure: Return Receipt Postcard

NOVEL STABLE PARACETAMOL-BASED LIQUID FORMULATIONS AND A METHOD FOR PREPARING THE SAME

FIELD OF THE INVENTION

The present invention relates to novel stable, liquid, analgesic formulations, containing paracetamol as main active ingredient, either in combination or not, with an analgesic derivative.

DISCUSSION OF THE PRIOR ART

It has been known for many years and notably from a paper of FAIRBROTHER J.E. entitled : Acetaminophen, published in Analytical Profiles of Drug Substances (1974), volume 3, pp. 1 - 109, that paracetamol in the presence of moisture, and all the more in aqueous solution, may be hydrolysed to yield p-aminophenol, which compound may itself be broken down into quinone-imine. The rate of decomposition of paracetamol is enhanced as the temperature is increased and upon exposure to light.

In addition, the instability of paracetamol in aqueous solution as a function of the solution's pH has been extensively described. Thus, according to a paper entitled "Stability of aqueous solutions of N-acetyl-p-aminophenol" (KOSHY K.T. and LACH J.L.J. Pharm. Sci., 50 (1961), pp. 113 - 118), paracetamol in aqueous solution is unstable, a fact which primarily correlates with hydrolysis both in acidic and basic environment. This breakdown process is minimal at a pH close to 6, the half-life of the product thus degraded namely being as high as 21.8 years at 25°C.

According to Arrhenius law and knowing the specific reaction constant as determined by these authors, the time needed to observe a 5% decrease in paracetamol concentration of an aqueous solution stored at 25°C at the optimal pH has been predicted to be 19 months. Besides hydrolysis, the paracetamol molecule separately undergoes another kind of decomposition

that involves formation of a quinone-imine that may readily polymerize with generation of nitrogen-containing polymers.

These polymers and in particular those stemming from N-acetyl-p-benzoquinone-imine have been further described as being the toxic metabolite of paracetamol, which is endowed notably with cytotoxic and hemolytic effect. The decomposition of this metabolite in aqueous medium is still more complex and gives rise to p-benzoquinone and hydroquinone (D. DAHLIN, J. Med. Chem., 25 (1982), 885 - 886).

In the current state of the art and in view of the quality control requirements specific to pharmaceutical practice regulations, the stability of paracetamol in aqueous solutions is thus insufficient and does not allow the formulation of liquid pharmaceutical compositions for injection. As a result, the successful preparation of liquid phamaceutical formulations for parenteral administration, based on paracetamol, has not been achieved.

A number of trials has been undertaken to slow down the decomposition of paracetamol in aqueous solution. Thus, in a paper entitled : Stabilization by ethylenediamine tetraacetic acid of amide and other groups in drug compound, (FOGG Q.G. and SUMMAN, A.M., J. Clin. Pharm. Ther., 17 : (1992), 107 - 109), it is stated that a 0.1% aqueous solution of paracetamol has a p-aminophen content resulting from hydrolysis of paracetamol, approximating 19,8% of the initial concentration of paracetamol, as observed after storage in the dark during 120 days. Addition of EDTA at a rate de 0.0075% brings down the decomposition rate to 7%. On the other hand, distilling an alkaline solution of paracetamol results in an ammonia concentration of 14%, in presence or not of 1000 ppm of ascorbic acid. Owing to its properties, ascorbic acid is indeed quite adapted to such stabilization. However, upon exposure to bright light, a paracetamol solution containing 1000 ppm of ascorbic acid does after all generate ammonia with a yield of 98%. In contrast, addition of EDTA (0.0075%) to such a solution cuts down decomposition rate, with an ammonia yield not higher than 14%.

Despite of such efforts, it has not been possible to prepare aqueous liquid solutions of paracetamol, in particular solutions for injection, having a guaranteed stability.

SUMMARY OF THE INVENTION

The present invention is aimed at solving the above stated problem in an appropriate manner. It is directed to stable pharmaceutical compositions of paracetamol in an aqueous solvent having added thereto a free radical antagonist. The aqueous solvent may be water or else aqueous mixtures containing water and a polyhydric compound such as polyethylene-glycol (PEG) 300, 400, 1000, 1540, 4000 or 8000, propylene glycol or tetraglycol. A water-soluble alcanol such as for example ethanol may also be used.

DETAILED DESCRIPTION OF THE INVENTION

Stability of the aqueous solutions mentioned above does not solely depend on the choice of a given carrier. It also depends on other variables, such as careful adjustment of pH, removal of oxygen dissolved in the carrier and addition of a free radical antagonist or a free radical scavenger.

Removal of dissolved oxygen is readily accomplished by bubbling an inert gas and preferably by bubbling nitrogen.

The appropriate free radical antagonist is chosen among the derivatives of ascorbic acid, those derivatives bearing at least a thiol functional group and straight chain or cyclic polyhydric compounds.

Preferred ascorbic acid derivatives are D- or L-ascorbic acid, an alkali metal ascorbate, an alkaline earth metal ascorbate or even still an aqueous medium-soluble ascorbic acid ester.

Free radical scavengers, bearing a thiol functional group may be an organic compound substituted by one or more thiol functional groups, of the aliphatic series such as cystein, acetylcystein, thioglycollic acid and salts thereof, thiolactic acid and salts thereof, dithiothreitol, reduced glutathion, thiourea, thioglycerol, methionine and mercaptoethane sulfonic acid.

The polyol used as a free radical scavenger is preferably a straight chain or a cyclic, polyhydroxy alcohol such as mannitol, sorbitol, inositol, isosorbide, glycerol, glucose and propylene-glycols.

Among free radical scavengers required pour stabilizing paracetamol, the ascorbic acid derivative currently preferred is sodium ascorbate. Preferred thiol functional group substitued derivatives are cystein, reduced-state glutathion, N-acetylcystein and mercaptoethane sulfonic acid.

It may appear as convenient to combine several free radical scavengers as far as they are water-soluble and mutually compatible. Especially convenient free radical scavengers are mannitol, glucose, sorbitol or even glycerol. These may be readily combined.

It may appear as convenient to add to the preparation one or a number of complexing agents to improve stability of the molecule since the active ingredient is sensitive to the presence of trace metals that eventually speed up its decay.

Complexing agents are exemplified by nitrilotriacetic acid, ethylene diamino tetraacetic acid, ethylene diamino N, N'-diacetic-N, N'-dipropionic acid, ethylene diamino tetraphosphonic acid, 2, 2'-(ethylene diamino)dibutyric acid, or ethylene-glycol bis(diaminoethyl ether) N, N, N', N'-tetraacetic acid and sodium or calcium salts thereof.

The complexing agent also acts to complex bivalent ions (copper, zinc, cadmium) that may be present and that have a negative influence of the aging of the formulation throughout storage.

The gas that is bubbled into the solution to drive out oxygen, may be nitrogen or carbon dioxide or still an inert gas. Nitrogen is favoured.

Isotonicity of the preparation may be achieved by adding an appropriate quantity of sodium chloride, glucose, levulose or postassium chloride, or calcium chloride, or calcium gluconoglucoheptonate, or mixtures thereof. The preferred isotonizing agent is sodium chloride.

The buffer used is a buffer compatible with parenteral administration in humans, the pH of which may be adjusted between 4 and 8. Preferred buffers

are based on alkali metal ou alkaline earth metal acetates or phosphates. A more preferred buffer is sodium acetate/hydrogeno phosphate adjusted to the required pH with hydrochloric acid or sodium hydroxide. The concentration of such a buffer may be comprised betwenn 0.1 and 10 mg/ml. The preferred concentration is confined in the range of 0.25 to 5 mg/ml.

On the other hand, preparations for injection have to be sterile and should lend themselves to heat treatment sterilization. It is known that in certain conditions, antioxidants such as glutathion are broken down [FIALAIRE A. et al., J. Pharm. Biomed. Anal., vol. 10, N° 6, pp. 457 - 460 (1992)]. The breakdown of reduced glutathion during heat treatment sterilization ranges from 40 to 77% depending on the selected temperature conditions. During such sterilization procedures, it is convenient to employ means capable of preserving the integrity of these antioxidants. Addition of complexing agents to aqueous solutions inhibits thermal decomposition of thiol derivatives, such as glutathion.

Liquid pharmaceutical compositions according to the invention are preferably compositions intended for injection. The paracetamol content of the solution may range from 2 mg/ml to 50 mg/ml in case of so called dilute solutions, i.e. that can be directly infused by intravenous route and from 60 mg/ml to 350 mg/ml where so-called concentrated solutions are considered, i.e. either intended for direct injection by intravelnous or intramuscular route, or intended to be diluted prior to slow infusion administration. The preferred concentrations are comprised between 5 and 20 mg/ml for dilute solutions and between 100 and 250 mg/ml for concentrated solutions.

Pharmaceutical compositions according to the invention may further contain another active ingredient that enhances the specific effet of paracetamol.

In particular, the pharmaceutical compositions according to the invention may contain a CNS-acting analgesic such as for example a morphinic analgesic.

The morphinic analgesic is selected among the morphinic derivatives of natural, semi-synthetic or synthetic origin and piperidine derivatives selected from the following list, which is no way intended to be exhaustive : buprenorphine, clramadol, codeine, dextromoramide, dextropropoxyphene, hydrocodone, hydromorphone, ketobemidone, levomethadone, levorphanol, meptazinol, methadone, morphine, nalbuphine, nicomorphine, dizocine, diamorphine, dihydrocodeine, dipipanone, methorphane, dextromethorphane.

Preferred morphinic derivatives are codeine sulfate or morphine hydrochloride.

The codeine or codeine derivative concentration, expressed in terms of codeine base, is comprised between 0.2% and 25% in relation to the paracetamol content. The preferred codeine derivative is codeine sulfate. The concentration thereof is set between 0.5 and 15% in relation to the paracetamol content

The morphine or morphine derivative concentration, expressed in terms of morphine base, is comprised between 0.05 and 5% in relation to the paracetamol content. The preferred morphine derivative is morphine hydrochloride the concentration of which is preferably set between 0.5 and 15% in relation to paracetamol content.

The compositions according to the invention may further have added thereto an anti-inflammatory agent such as of the of AINS type and in particular a phenylacetic acid compound. Such agents are exemplified by ketoprofen, flurbiprofen, tiaprofenic acid, niflumic acid, diclofenac or naproxen.

Compositions according to the invention may in addition incorporate an antiemetic either a CNS-acting neuroleptic such as haloperidol or chlorpromazine or metopimazine or of the gastrokinetic-mediated type such as metochlopramide or domperidone or even a serotoninergic agent.

Compositions in accordance with the invention may further incorporate an anti-epileptic drug such as sodium valproate, clonazepam, carbamazepine or phenytoin.

It may also be possible to combine paracetamol with a corticosteroid such as for example prednisone, prednisolone, methyl prednisone, dexamethasone, betametasone or an ester thereof.

Paracetamol can further be combined with a tricyclic antidepressant such as amitriptiline, imipramine, clomipramine.

Anti-inflammatory agents may be included in concentrations ranging from 0.100 g to 0.500 g per 1000 ml of formulated product.

In case of concentrated solutions

The water content expressed in percentage is preferably in exces of 5% of the total volume and more preferably comprised between 10 and 65%.

The quantity of propylene glycol formulated in percentage is preferably in excess of 5% and more preferably comprised between 20 and 50%.

The PEG used is preferably PEG 300, PEG 400, PEG 1000, Peg 1540 or PEG 4000. Concentrations used are comprised between 10 and 60% in weight. PEG 300 and PEG 400 are further preferred. Preferred concentrations range from 20 to 60%.

Ethanol concentrations range from 0 to 30% of total volume and preferably range from 0 to 20%.

Tetraglycol concentrations used do not exceed 15% to allow for maximal quantities that can daily be received by parenteral administration viz. 0.7 ml/kg of body weight.

Glycerol concentration varies from 0.5 to 5% as a function of the viscosity of the medium suitable for use depending on the administration route.

In case of dilute solutions

The quantity of water used given in percentage is preferably in excess of 20% of the total volume and preferably is comprised between 25 and 100%.

The quantity of propylene-glycol employed given in percentage is preferably comprised between 0 and 10%.

The PEG used is preferably PEG 300, PEG 400, or PEG 4000 with PEG 4000 being most preferred. Preferred concentrations range from 0 to

10%. Tetraglycol concentrations used do not exceed 5%. In preference, they are comprised between 0 and 4%

The ascorbic acid or ascorbic acid derivative concentration which is used, is preferably more than 0.05 mg/ml and more desirably, comprised between 0.15 mg/ml and 5 mg/ml. Higher quantities may indeed be used, without exceeding the solubility limits Higher ascorbic acid or ascorbic acid derivative concentration are administered to human beings for prophylactic or therapeutic purposes.

Thiol derivative concentration is comprised between 0.001% and 30% and more desirably, comprised between 0.005% and 0.5% for dilute solutions, and between 0.1% and 20% for concentrated solutions.

The pH of the solution is desirably adjusted taking into consideration the optimal stability of paracetamol in aqueous solution, i.e. at a pH around 6.0.

The thus prepared composition may be packaged in glass sealed vials, or in stoppered glass vials or in bottles made of a polymer material such as polyethylene, or in soft material bags made from polyethylene, polyvinyl chloride or polypropylene.

The composition may be sterilized by heat treatment, for example at 121°C during 20 minutes or else by sterile filtration.

Currently preferred compositions in accordance with the invention have the following ingredients :

Concentrated solutions

Ingredient	Injection solution of paracetamol alone (per ml)	Injection solution of paracetamol associated to a morphinic compound (per ml)	
		codein	morphine
paracetamol	0.160 g	0.160 g	0.160 g
codein sulfate.$3H_2O$	-	0.0036 g	-
Morphine hydrochloride.$3H_2O$	-	-	0.00037
Propylene glycol	0.270 ml	0.270 ml	0.270 ml
PEG 400	0.360 ml	0.360 ml	0.360 ml
Sodium acetate	0.002 g	0.002 g	0.002 g
Reduced glutathion	0.002 g	0.002 g	0.002 g
Hydrochloric acid 1 N	q.s. pH 6.0*	q.s. pH 6.0*	q.s. pH 6.0*
Water for injection	q.s. 1000 ml	q.s. 1000 ml	q.s. 1000 ml
Nitrogen	q.s.f. bubbling	q.s.f. bubbling	q.s.f. bubbling

* The pH specified above is the actual pH that has been measured by a pH-meter after obtaining a 5 fold dilution of the solution with distilled water. It will be noted that the apparent pH of the pure solution is different.

Using this solution composed of a solvent mixture constituted by 30% of propylene-glycol, by 40% of polyethylene-glycol 400 and by 30% of water (solution n° 20), it is possible to dissolve about 200 mg/ml of paracetamol at 20°C. Choosing a concentration of 160 mg/ml allows one to be sure that no recristallization will occur, notably at low temperatures. In such situations, a volume of 6,25 ml of said solution contains 1000 mg of paracetamol.

Dilute solutions

Ingredient	Injection solution of paracetamol alone (per ml)	solution of paracetamol associated to codein (per ml)	
		Such morphinic compound is codein	Such morphinic compound is morphine
paracetamol	0.0125 g	0.125 g	0.125 g
codein sulfate.$3H_2O$	-	0.00018 g	-
Morphine hydrochloride.$3H_2O$	-	-	0.000019 g
Mannitol	0.025 g	0.025 g	0.025 g
Sodium hydrogen phosphate dihydrate	0.0025 g	0.00025 g	0.00025 g
Sodium chloride	0.002 g	0.002 g	0.002 g
Disodium ethylene diamino tetraacetate	0.0001 g	0.0001 g	0.0001 g
Hydrochloric acid or sodium hydroxide	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Water for injection	q.s.f. 1000 ml	q.s. f. 1000 ml	q.s. f. 1000 ml
Nitrogen	q.s. f. bubbling	q.s. f. bubbling	q.s. f. bubbling

The compositions according to the invention find therapeutic applications as pain relief drugs. For moderate pain, the solutions merely contain paracetamol. For acute pain, the solutions further contain a morphinic analgesic. Furthermore, the paracetamol solutions exert antipyretic activity.

The following examples are given by way of illustration and not by limitation.

EXAMPLE I

Determination of the optimal solvent mixture

1.1 Concentrated solutions

Increasing quantities of paracetamol were introduced in the solvent mixtures. The dissolution rate of paracetamol increases with rise in temperature, so that the solubility tests in the individual media were run by heating the solvent mixture to 60°C. Après dissolution was judged complete, the solutions were stored for 72 hours either at 25°C or 4°C.

The solubility values are listed in the following table :

Test n°	Water (ml)	Propylene-glycol (ml)	PEG 400 (ml)	Ethanol	Tetraglycol (ml)	Solubility at +4°C (mg/ml)	Solubility at +25°C (mg/ml)
1	0.3	0.4	0.3	-	-	110	130
2	0.4	0.3	0.3	-	-	110	130
3	0.15	0.3	0.4	-	0.15	190	230
4	0.5	-	0.5	-	-	110	150
5	0.4	0.3	0.2	0.1	-	< 110	120
6	0.5	0.3	0.1	0.1	-	< 100	130
7	0.4	0.4	0.1	0.1	-	< 100	150
8	0.6	0.3	0.2	-	-	< 100	120
9	0.6	0.3	0.2	-	-	< 100	< 100
10	0.5	0.4	0.1	-	-	< 100	< 100
11	0.55	0.3	0.05	0.1	-	< 100	< 100
12	0.45	0.4	0.05	0.1	-	< 100	120
13	0.65	0.3	0.05			< 100	< 100
14	0.55	0.3	0.05	-	-	< 100	< 100
15	0.4	0.4	0.2	-	-	< 100	< 150
16	0.45	0.45	0.1	-	-	< 100	< 110
17	0.4	0.2	0.4	-	-	160	200
18	0.5	0.2	0.3	-	-	160	160
19	0.5	0.1	0.3	-	-	100	190
20	0.3	0.3	0.4	-	-	190	200
21	0.3	0.2	0.35	-	0.15	160	210
22	0.25	0.25	0.35	-	0.15	170	220

The solubility values of the solvent mixtures do not increase in a consistent manner with increasing temperature. Solubility is not enhanced if ethanol is added.

In addition, due to oversaturation phenomena which are observed in such solutions, notably in media containing PEG, a delayed recrystallization was noted subsequent to cooling. In these conditions, the solutions under study were kept for 14 days at 20°C, then there was added, to the solutions displaying no cristals following this time interval, a paracetamol germ cristal in order to elicit cristallization of potentially oversaturated solutions. Finally, it was found that solutions n° 20 and n° 3 have the highest solubility with respect to paracetamol, which threshold was comprised between 160 mg/ml and 170 mg/ml depending on temperature.

1.2 Dilute solutions

Paracetamol in quantities well exceeding the solubility threshold was introduced in the solvent mixtures previously warmed to 30°C. After stirring and cooling at 20°C, the solutions were filtered The paracetamol content of these solutions was determined by reading the absorbance at 240 nm of a 1:200 dilution of the filtrate.

The results are recorded in the following tables.

Type of solution (unless otherwise stated, the main solvent is distilled water)	concentration of paracetamol (mg/50 ml)
Water	720
5% Glucose	710
4.82% levulose	730
7% mannitol	680
5% sorbitol	685
0.9% sodium chloride	615
10% Calcium gluconoglucoheptonate	670
Lestradet's solution (5% glucose, 0.2% sodium chloride, 0,15% potassium chloride, 1.1% calcium gluconoglucoheptonate)	730
Ringer's solution (0.7% sodium chloride, 0.1% potassium chloride, 0.1% sodium chloride)	730
Ringer's solution- Phosphate (0.7% sodium chloride, 0.182% monopotassium phosphate, 0.182% calcium chloride)	710
Ringer's solution-acetate (0.7% sodium chloride, 0.131% potassium acetate, 0.013% calcium chloride)	715
Urea 0.3 M	725

Type of solution (the following solutions were prepared in Ringer's solution)	concentration of paracetamol (mg/50 ml)
Pure Ringer's solution	735
4.0% PEG 4000 + 1.0% propylene-glycol + 0.5% ethanol	905
4.0% PEG 4000 + 1.0% propylene-glycol + 1.0% ethanol	905
4.0% PEG 4000 + 1.0% propylene-glycol + 2.0% ethanol	930

Type of solution (the following solutions were prepared in 0.9% sodium chloride solution)	concentration of paracetamol (mg/50 ml)
0.9% sodium chloride	615
+ 0.6% tetraglycol	640
+ 1.2% tetraglycol	680
+ 3.0% tetraglycol	720
1.0% PEG 4000	630
1.0% PEG 4000 + 0.6% tetraglycol	660
1.0% PEG 4000 + 1.2% tetraglycol	710
3.0% PEG 4000 + 2.0% tetraglycol	950

Paracetamol solubility is increased by the presence of PEG.

Solubilities of paracetamol in mixtures of PEG 4000 and 0.9% sodium chloride solutions were determined in distilled water, at concentrations ranging from 0 to 7%, as a function of temperature.

The results are given in the following table :

	Solvent volume (ml) required to dissolve 1000 mg of paracetamol as a function of temperature				
PEG 4000 concentration (%/vol.) in 0.9% sodium chloride solution	4°C	17°C	22°C	30°C	42°C
0%	130	92	80	65	42
1%	99	78	67	63	47
2%	91	72	63	59	45
3%	80	64	56	54	41
4%	82	62	57	49	36
5%	79	59	51	46	34
7%	78	61	48	42	30

4.1 Concentrated solution

	Quantity	
Ingredient	Solution without nitrogen bubbling	solution subjected to nitrogen bubbling
Paracetamol	0.160 g	0.160 g
Propylene-glycol	0.270 ml	0.270 ml
PEG 400	0.360 ml	0.360 ml
Sodium hydroxide or HCl 1N	q.s. pH 6.0	q.s. pH 6.0
Nitrogen	none	q.s. f. purging and filling
Water for injection	q.s. f. 1000 ml	q.s. f. 1000 ml

Solution 20 containing paracetamol in a quantity of 160 mg/ml, adjusted to pH 6,0 by sodium hydroxide or hydrochloric acid 1 N, was either subjected or not subjected to nitrogen gas bubbling. Tightly stoppered and capped vials packed by dispensing 10 ml of such solutions under nitrogen atmosphere or air, were sterilized by autoclaving at 121°C during 20 minutes. The percentage of secondary peaks was then measured by liquid chromatography with respect to the main peak of paracetamol, as well as was the pink color strength by reading the solution absorbance by absorption spectrophotometry at peak absorbance wavelength, that is 500 nm.

Results

Solution tested	Secondary peaks in % of main peak of paracetamol	absorbance of the solution at 500 nm
Autoclaved solution packed without nitrogen	0.054	0.08
Autoclaved solution packed under nitrogen	0.036	0.03

It is therefore seen that the difference in color of the solution packed under nitrogen is very striking

In order to check if 0% and 1% PEG-paracetamol solutions remain clear under cold storage, the following solutions were prepared :

Ingredient	Solution without PEG	Solution with PEG added
Paracetamol	1 g	1 g
PEG 4000	-	1 g
0.9% Sodium chloride solution in water for injection	q.s. 125 ml	q.s. 100 ml

After storage of these solutions at 4°C during 10 days, none of the vials tested showed cristallization. Presence of PEG is therefore not mandatory if the solutions are to remain clear throughout the time interval studied.

EXAMPLE II

TESTS CONDUCTED FOR CHARACTERIZING PARACETAMOL BREAKDOWN IN SOLUTION

2.1 Demonstrating paracetamol instability in solution

A paracetamol solution in water or in solution n° 20 shows rapidly a pink color upon exposure to light or storage at high temperature. At 50°C, color development occurs in 2 weaks time. Appearance of such color tinge correlates with an increase in solution absorbance at a peak absorbance wavelength of 500 nm. According to the paper of Fairbrother mentioned above, exposure of paracetamol to moisture can result in hydrolysis with formation of para-aminophenol, followed by oxydation, with appearance of a pink color, typical of the production of quinoneimine.

2.2 Identifying the breakdown products of paracetamol

In aqueous or partially aqueous solutions, p-aminophenol is not detected during storage. Rapid production of colored products having a pink tinge is noted, the reaction rate being a function of temperature and light. In course of time, such derivatives are increasingly dark and evolutes to brown color.

All occurs as if, in contrast to what has been reported in the litterature, the breakdown of paracetamol first involves an oxydative process followed by hydrolysis. According to this theory, paracetamol may react with an oxidant present in solution, for example oxygen dissolved in the aqueous layer. This mechanism may involve the production of free radicals resulting in molecular coupling, a fact that may account for the production of colored derivatives evoluting in color from pink to brown.

2.3 Tests for demonstrating inhibition of free radical production

A typical reaction involving the production of free radicals involves adding a 30% aqueous solution of hydrogen peroxide and a copper pentahydrate solution at a concentration of 62.5 mg/ml, to a 1.25% aqueous solution of paracetamol. In a matter of minutes, there develops a color reaction resulting in a color shift from yellow to dark brown. The color intensity observed decreases if free radical scavengers or glycerol are prior added to the paracetamol solution. Color intensity is a function of type of the type of free radical scavenger added, in the following decreasing order as judged by color intensity :

Paracetamol alone > paracetamol + N-acetylcysteln > paracetamol + cystein > paracetamol + sorbitol > paracetamol + mannitol > paracetamol + glycerol.

EXAMPLE III

Stabilizing paracetamol solution by selecting the pH that allows maximal stability

3.1 Concentrated solution

Solution tested

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Sodium hydroxide 1N or Hydrochloric acid 1N q.s.f.	pH 7.0 - 8.0 - 9.0 - 9.5 - 10.0 corresponding to actual pH : pH 5.8 - 6.7 - 7.1 - 7.5 - 8.0 - 8.5
Nitrogen q.s.f.	purging and filling
Water for injection	q.s. 1000 ml

Solution 20 containing paracetamol in a concentration of 160 mg/ml was adjusted to different pH's : the apparent pH is given in comparison to actual pH (between parenthesis) after a 5 fold-dilution : 7,0 (5,8) - 8,0 (8,7) - 8,5 (7,1) - 9,0 (7,5) - 9,5 (8,0) - 10.0 (8,5) using a sodium hydroxide or normal hydrochloric acid solution. Vials that had been filled under nitrogen atmosphere by dispensing 10 ml of such solutions, tightly stoppered and capped, were sterilized by autoclaving at 121°C for 20 minutes, and then in every case exposed, either to a temperature of 105°C in the dark for 72 hours, or to a radiation of an actinic light at 5000°K and 25°C during 264 hours.

Results

After autoclaving, only the solution adjusted to pH 10 shows a pink tinge. After storage at 105°C for 72 hours, absorbance at 500 nm as well as the concencentration of breakdown products of paracetamol were minimal in the pH range from 7,5 to 9,5. Upon storage in the presence of light, the color strength is enhanced as the pH is increased. Color development is extremely weak at pH 7,0 (actual pH 5,8). Neither the paracetamol content, nor the beakdown products are affected by pH.

3.2 Diluted solution

Solution tested

Ingredient	Quantity
Paracetamol	0.008 g
Sodium chloride	0.0067 g
Disodium phosphate dihydrate	0.0012 g
5% Citric acid q.s.f.	pH 5.0 - 6.0 - 7.0
Nitrogen q.s.f.	bubbling and filling
Water for injection	q.s.f. 1000 ml

The aqueous solution diluted and buffered having a paracetamol content of 8 mg/ml was adjusted to different pH values : pH 5,0 - 7,0 using a citric acid solution.

Vials that had been packed under nitrogen atmosphere by dispensing 10 ml of such solutions, were tightly stoppered and capped, sterilized by autoclaving at 121°C for 20 minutes, and then in every case exposed to 70°C in the dark during 231 hours.

Results

Following autoclaving, only the solution adjusted to pH 7 shows a pink color. After storage, this same solution displays the brightest pink color. At pH 6,0 and 5,0. the solutions are faintly colored.

EXAMPLE IV

Stabilization of paracetamol in solution by oxygen removal through nitrogen bubbling

4.2 Diluted solution

Solution Tested

	Quantity	
Ingredient	Solution without nitrogen bubbling	solution subjected to nitrogen bubbling
Paracetamol	0.008 g	0.008 g
Sodium chloride	0.008 g	0.008 g
Disodium phosphate dihydrate	0.001 g	0.001 g
5% Citric acid	q.s.f. pH 6.0	q.s.f. pH 6.0
Nitrogen	none	q.s.f. purging and filling
Water for injection	q.s.f. 1000 ml	q.s.f. 1000 ml

The diluted aqueous solution containing paracetamol is adjusted to pH 6,0 by means of a citric acid solution.

Vials that had been filled under a nitrogen atmosphere by dispensing 10 ml of such solutions, were tightly stoppered and capped and then stored inside an incubator at 98°C for 15 hours.

The percentage of secondary peaks in relation to the main peak of paracetamol was measured by liquid chromatography, so was the pink color strength by reading the solution absorbance by absorbance spectrophotometry at a peak absorption wavelength, that is 500 nm.

Results

Solution tested	Secondary peaks in % of paracetamol main peak	Solution absorbance at 500 nm
Solution packed without nitrogen atmosphere	1.57	0.036
Solution packed under nitrogen atmosphere	0.44	0.016

The pink color of the solution packed under nitrogen atmosphere is considerably fainter than that observed for the solution obtained after sterilization under nitrogen of the solution packed without nitrogen.

EXAMPLE V

Stabilizing solutions of paracetamol by adding free radical antagonists

5.1 Concentrated solution

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Hydrochloric acid 1N or NaOH 1N q.s.f.	pH 6.0
Free radical scavenger (see quantitative results)	q.s.f. (see quantitative results)
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The solutions thus prepared are divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. After autoclaving at 121°C for 20 minutes, the vials were stored for 48 hours, either in the presence of actinic light at 5500°K at room temperature or at 70°C in the dark. The preparation was examined for any change in color.

Results

Free radical scavenger	Concentration	Appearance of the solution upon exposure to light Color Intensity	Appearance of solution at 70°C Color intensity
No scavenger	-	pink (+)	pink (++)
Sodium disulfite	0.295 mg/ml	colorless	colorless
Sodium ascorbate	1.0 mg/ml	yellow (+)	yellow (+)
Reduced glutathion	1 mg/ml	colorless	colorless
Reduced glutathion	8 mg/ml	colorless	colorless
Cystein hydrochloride	1 mg/ml	cloudy	cloudy
α-monothioglycerol	1 mg/ml	colurless	colorless
Dithiothreitol	1 mg/ml	colorless	colorless
Mannitol	50 mg/ml	colorless	colorless

5.2 Dilute solution

Solutions tested

Ingredient	Quantity		
	Formulation A	Formulation B	Formulation C
Paracetamol	0.008 g	0.01 g	0.0125 g
Sodium chloride	0.008 g	0.008 g	0.00486 g
Disodium phosphate dihydrate or sodium acetate	0.001 g	0.001 g	0.00125 g
Hydrochloric acid	q.s. ph 6.0	q.s. pH 6.0	q.s. pH 5.5
C.R.L.	q.s. (see quantitative results)		
Nitrogen q.s.f.	purging and filling		
Water	q.s.f. 1000 ml		

The solutions thus prepared were divided in 10 ml, 100 ml or 80 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. The preparation was examined for any pink color development

After autoclaving at 121°C for 20 minutes, the vials were stored for 48 hours, either in the presence of actinic light at 5500°K at room temperature or at 70°C in the dark (formula A).

After autoclaving at 124°C for 7 minutes, the vials were stored for 48 hours at room temperature in the dark (formulation B and C). The preparation was examined for any pink shift and the paracetamol as well as CRL were measured where a thiol derivative was used.

Results (CRL = free radical scavenger)

C.R.L used	Concentration	Solution appearance upon exposure to light		Solution appearance at 70°C	
		color	strength	color	strength
No C.R.L	-	pink	(+)	pink	(++)
Thiourea	0.5 mg/ml	colorless		colorless	
Dithiothreitol	1 mg/ml	colorless		colorless	
α-monothioglycerol	1 mg/ml	colorless		colorless	
gluthathion	1 mg/ml	colorless		colorless	
Sodium ascorbate	0.2 mg/ml	pink	(+)	pink	(+)
	0.4 mg/ml	colorless		yellow	(+)
	0.6 mg/ml	pink	(+)	yellow	(+)
	1.0 mg/ml	colorless		yellow	(+)
Cystein hydrochloride	0.05 mg/ml	colorless		colorless	
	0.1 mg/ml	colorless		colorless	
	0.25 mg/ml	colorless		colorless	
	0.5 mg/ml	colorless		colorless	
	0.75 mg/ml	colorless		colorless	
	1 mg/ml	colorless		colorless	
	2 mg/ml	colorless		colorless	
	5 mg/ml	colorless		colorless	

C.R.L used	Concentration	Solution appearance		Dosages (in % of theoretical value)	
		color	strength	C.R.L.	paracetamol
Cystein hydrochloride monohydrate	0.2 mg/ml	colorless		80%	99.2%
Cystein hydrochloride monohydrate	0.5 mg/ml	colorless		96%	99.6%
N-acetylcystein	0.2 mg/ml	colorless		88%	99.2%
Mannitol	20 mg/ml	colorless			
Mannitol	40 mg/ml	colorless			
Mannitol	50 mg/ml	colorless			
Glucose	50 mg/ml	colorless			

EXAMPLE VI

Stabilization of solutions of paracetamol containing a morphinic compound by addition of a free radical scavenger

6.1 Concentrated solution

Solutions tested

Ingredient	Quantity
Paracetamol	0.160 g
Codein phosphate	0.008 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Hydrochloric acid 1N q.s.	q.s. pH 6.0
Free radical scavenger	q.s. (see quantitative results)
Water for injection	q.s.f. 1000 ml

The solutions thus prepared were divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with a removable aluminium cap. After autoclaving at 121°C for 20 minutes, the vials were stored for 48 hours either under actinic light at 5500 °K at room temperature, or at 70°C in the dark. The preparation was inspected for any change in color.

Results

Free radical scavenger	Concentration	Solution apperance upon exposure to light		Solution apperance at 70°C	
		color	strength	color	strength
No free radical scavenger	-	pink	(+)	pink	(++)
Sodium disulfite	0.295 mg/ml	yellow	(+)	yellow	(++)
Sodium ascorbate	1.0 mg/ml	yellow	(++)	yellow	(+++)
reduced glutathion	1 mg/ml	yellow	(+)	amber yellow	(+++)
	8 mg/ml	colorless		yellow	(++)
	16 mg/ml	colorless		yellow	(+)
Dithiothreitol	1 mg/ml	violet pink	(+++)	violet pink	(++++)
Sodium hypophosphite	5 mg/ml	pink	(+)	pink	(++)

6.2 Dilute solutions

Solutions tested

Ingredient	Quantity
Paracetamol	0.008 g
Codein phosphate	0.0004 g
Sodium chloride	0.008 g
Disodium phosphate dihydrate	0.0015 g
Hydrochloric acid	q.s.f. pH 6.0
Free radical scavenger	q.s. (see results)
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The solutions thus prepared were divided in 10 ml capacity vials, stoppered with a Bromobutyl stopper and capped with an aluminium cap. After autoclaving at 121°C for 20 minutes, the vials were stored for 48 hours, either under actinic light at 5500°C at room temperature, or at 70°C in the dark. The preparation was examined for any change in color.

For the solution not containing any free radical scavenger and for the solution containing 0.5 mg/ml of cystein hydrochloride as free radical antagonist, paracetamol as well as codein are measured by high performance liquid chromatography, immediately after autoclaving, in comparison with identical solutions not subjected to autoclaving.

Appearence scoring of the solutions

Free radical scavenger	Concentration	Solution appearance upon exposure to light		Solution appearance at 70°C	
		color	strength	color	strength
No free radical scavenger	-	pink	(+)	pink	(+)
Sodium disulfite	0.295 mg/ml	colorless		colorless	
Dithiothreitol	0.5 mg/ml	colorless		colorless	
Monothioglycerol	0.5 mg/ml	grey		grey	
Reduced glutathion	2.0 mg/ml	colorless		colorless	
N-acetylcystein	2.0 mg/ml	grey	(+)	grey	(+)
Cystein hydrochloride	0.05 mg/ml	colorless		pink	(+)
	0.1 mg/ml	colorless		colorless	
	0.25 mg/ml	colorless		colorless	
	0.5 mg/ml	colorless		colorless	
	0.75 mg/ml	colorless		colorless	
	1.0 mg/ml	colorless		colorless	
	2.0 mg/ml	colorless		colorless	
	5.0 mg/ml	colorless		colorless	

Assay results of paracetamol and codein

Solution tested	Ingredient assayed	non sterilized solution	after sterilization
Solutions with no free radical scavenger added	paracetamol codein	0.0078 g/ml 0.00043 g/ml	0.0077 g/ml 0.00042 g/ml
Solution containing 0,5 mg/ml of cystein hydrochloride	paracetamol codein	0.0082 g/ml 0.00042 g/ml	0.0081 g/ml 0.00042 g/ml

There is noted the lack of color development one one hand and excellent preservation of the active ingredients after heat treatment sterilization on the other hand.

EXAMPLE VII

Biological tolerance to the preparation

7.1 Hematological tolerance

Tested solutions

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The solution pH was not adjusted. The apparent pH is 7.6, corresponding to an actual pH of 6.5.

Whole human blood is incubated with the solution under study, in equal proportions by volume. 2 ml were drawn at 10 minutes intervals and centrifuged for 5 minutes at 5000 rpm. 100 µl of the supernatant were diluted in 1 ml of distilled water. The absorbance of this solution was determined against a water blank at 540 nm, peak absorption wavelength of hemoglobin.

The study was run in comparison with a negative control (physiological saline) and a positive control (pure water for injection)

Results

The absorbances of the individual solutions after different incubation periods are provided in the following table :

Solution	T0	10 min	20 min	30 min	40 min	50 min	60 min
Water p.p.i	2.23	2.52	2.30	2.37	2.38	2.33	2.36
Physiological saline	0.04	0.05	0.05	0.05	0.04	0.05	0.04
Sol. Tested	0.09	0.19	0.27	0.25	0.24	0.24	0.25

No hemolysis was detected.

7.2 Muscular tolerance

Solution tested

Ingredient	Quantity
Paracetamol	0.160 g
Propylene-glycol	0.270 ml
PEG 400	0.360 ml
Nitrogen q.s.f.	purging and filling
Water for injection	q.s.f. 1000 ml

The pH of this solution was not adjusted. Apparent pH is equal to 7,6.

Sprague-Dawley rats, weighing between 260 g and 450 g were anesthesized with an i.p. injection of ethyl carbamate (2 ml/kg of a 50% aqueous solution). The extensor digitorum longus muscle was dissected from the right or left hind leg, and placed in buffer medium having the following composition :

Ingredient	Quantity
Sodium chloride	6.8 g
Potassium chloride	0.4 g
Dextrose	1.0 g
Sodium bicarbonate	2.2 g
Phenol red (sodium salt)	0.005 g
Distilled water q.s f	1 liter
Hydrochloric acid 1N q.s.f.	pH 7.4

The muscle is transiently fixed to a board and maintained in position by tendons. The test product was injected in an amount of 15 µl by means of a 25 µl-capacity Hamilton seringe n° 702. The muscle is then placed over a grit and immersed in the buffer solution kept at 37°C with carbogen bubbling throughout the incubation period. At 30 minutes intervals, the muscles were introduced in a tube containing fresh buffer at 37°C. The procedure was repeated 4 times. The buffer solution hence incubated is assayed for creatine kinase activity.

The study was run in parallel with :

- muscle alone not subjected to injection (blank)
- needle alone (introducing the needle without product injection)
- physiological saline

Triton X-100 solution (negative controls)

- solution 20

solution 20 + paracetamol 160 mg/ml.

Creatine kinase was measured using a Hitachi 704 model analyzer in conjunction with a reagent kit sold under tradename high performance Enzyline CK NAC 10 (Biomérieux).

Results

The creatine kinase activity (IU/l) of the individual solutions after variable incubation periods are provided in the table given hereinafter :

Solution tested	30 min	60 min	90 min	120 min	Total
Muscle alone	23 ± 6	24 ± 12	15 ± 7	13 ± 5	75
Needle alone	35 ± 6	33 ± 10	20 ± 4	18 ± 7	106
Physiological saline	30 ± 6	10 ± 12	17 ± 6	23 ± 4	100
Triton-X	1802 ± 2114	1716 ± 978	155 ± 89	289 ± 251	14962
Solution 20 (excipients)	71 ± 24	89 ± 40	39 ± 27	62 ± 39	261
Solution 20 + paracetamol	141 ± 40	150 ± 60	68 ± 63	34 ± 24	393

No necrosis signs were recorded using the composition according to the invention as no significant difference between the results of test and excipient solutions was noted.

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WHAT IS CLAIMED IS

1. Novel paracetamol-based, stable, liquid formulations in an aqueous solvent.

2. Novel stable, paracetamol-based, liquid formulations according to claim 1, wherein the aqueous solvent is a mixture containing water and a polyhydric compound or a water-soluble alcanol.

3. Novel stable, paracetamol-based, liquid formulations according to claim 1 and claim 2, in an aqueous solvent, wherein the aqueous solvent is deoxygenated by bubbling a water-insoluble inert gas.

4. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 3, wherein the pH of the aqueous solvent is adjusted by means of a buffering agent, in the range of 4 to 8.

5. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 4, wherein the buffering agent yields a pH of approximately 6.0.

6. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 4, wherein the formulations further incorporate at least one free radical-scavenger.

7. Novel stable, paracetamol-based, liquid formulations according to claim 6, wherein the free radical-scavenger is chosen among ascorbic acid derivatives, organic compounds bearing at least one thiol functional group, and polyhydric compounds.

8. Novel stable, paracetamol-based, liquid formulations according to claim 6 or claim 7, wherein the ascorbic acid derivatives are chosen from the group of D-ascorbic acid, L ascorbic acid, alkali metal ascorbates, alkaline earth metal ascorbates and ascorbic acid esters that are soluble in aqueous medium.

9. Novel stable, paracetamol-based, liquid formulations according to claim 6, wherein the organic compound bearing the thiol functional group is chosen among the compounds of the aliphatic or alicyclic series, bearing one or a number of thiol functional groups.

10. Novel stable paracetemol-based liquid formulations according to claim 6 and claim 9, wherein the compound bearing the thiol functional group is chosen from the group of thioglycolic acid, thiolactic acid, dithiothreitol, reduced glutathion, thiourea, α-thioglycerol, cystein, acetylcystein and mercaptoethane sulfonic acid.

11. Novel stable, paracetamol-based, liquid formulations according to claim 6 and claim 7, wherein the polyhydric compound is an aliphatic polyhydric alcohol containing from 2 to 10 carbon atoms.

12. Novel stable, paracetamol-based, liquid formulations, acording to claim 6 and 7, wherein the polyhydric compound is a sugar or a cyclic or straight chain-glucitol, having from 2 to 10 carbon atoms, selected among mannitol, sorbitol, inositol and glucose.

13. Novel stable, paracetamol-based, liquid formulations according to claim 12, wherein the polyhydric compoun is glycerol.

14. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 13, further comprising at least one complexing agent.

15. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, wherein the paracetamol concentration ranges from 2 mg to 50 mg/ml as for diluted solutions.

16. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, wherein the paracetamol concentration ranges from 60 mg to 350 mg/ml as for concentrated solutions.

17. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, wherein an appropriate quantity of isotonizing agent is added to the preparation.

18. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, wherein solutions intended for parenteral administration are sterilized by heat treatment

19. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising a central nervous system acting analgesic such as for example a morphinic analgesic.

20. Novel stable, paracetamol-based, liquid formulations according to claim 19, wherein the morphinic analgesic is a morphinic compound of natural, semi-synthetic or synthetic origin, a phenylpiperidine compound, a nipecotic acid compound, a phenylcyclohexanol compound or a phenylazepine compound.

21. Novel stable, paracetamol-based, liquid formulations according to claim 19, wherein the morphinic analgesic is present in a quantity ranging from 0,05 to 5% of paracetamol in case of morphine and from 0,2 to 2,5% in case of codeine.

22. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising an anti-inflammatory agent such as that of the phenylacetic acid type.

23. Novel stable, paracetamol-based, liquid formulations according to claim 22, wherein the anti-inflammatory agent is ketoprofen .

24. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising an antiemetic.

25. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising an antiepileptic.

26. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising a corticosteroid.

27. Novel stable, paracetamol-based, liquid formulations according to anyone of claims 1 to 14, further comprising a tricyclic antidepressant.

ABSTRACT

Novel stable paracetamol compositions for use in therapeutic chemistry and specifically galenic pharmacy are disclosed. The compositions contain a solution of paracetamol in an aqueous solvent combined with a buffer having a pH of 4 to 8, and a free radical capturing agent. A water-insoluble inert gas is carefully bubbled through the aqueous solvent to remove oxygen from the medium. Said compositions may also be combined with a centrally or peripherally acting analgesic agent, and are provided as injectable compositions for relieving pain.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Attorney Docket Number	GEI-061
First Named Inventor	F. DIETLIN et al
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

[X] Declaration Submitted with Initial Filing OR [ ] Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

NOVEL STABLE LIQUID PARACETAMOL COMPOSITIONS, AND METHOD FOR PREPARING SAME

(Title of the Invention)

the specification of which

[ ] is attached hereto

OR

[X] was filed on (MM/DD/YYYY) August 5, 1997 as United States Application Number or PCT International Application Number PCT/FR97/01452 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
96/09858	France	8/5/96	[ ]	[ ]	[X]
PCT/FR97/01452	France	8/5/97	[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any:			A petition has been filed for this unsigned inventor		
Given Name	DANIELE	Middle Initial		Family Name	FREDJ
Suffix e.g. Jr.					
Inventor's Signature	D. Fredj Daniele Fredj			Date	20/4/1998
Residence: City	Gif-sur-Yvette	State		Country	France FRX
Citizenship	French				
Post Office Address	13 bus, chemin des Rougemonts				
Post Office Address					
City	Gif-sur-Yvette	State		Zip	F-91190
Country	France				

Name of Additional Joint Inventor, if any:			A petition has been filed for this unsigned inventor		
Given Name		Middle Initial		Family Name	
Suffix e.g. Jr.					
Inventor's Signature				Date	
Residence: City		State		Country	
Citizenship					
Post Office Address					
Post Office Address					
City		State		Zip	
Country					

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Given Name		Middle Initial		Family Name	
Suffix e.g. Jr.					
Inventor's Signature				Date	
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Citizenship					
Post Office Address					
Post Office Address					
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Suffix e.g. Jr.					
Inventor's Signature				Date	
Residence: City		State		Country	
Citizenship					
Post Office Address					
Post Office Address					
City		State		Zip	
Country					

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

(January 1997)

Please type a plus sign (+) inside this box → [+]

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian	19,683	4	
Jordan B. Bierman	18,629		
Donald C. Lucas	31,275		
Bierman, Muserlian and Lucas	18,818		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	Bierman, Muserlian and Lucas				
Address					
Address	600 Third Avenue				
City	New York	State	New York	ZIP	10016
Country	U.S.A.	Telephone	(212) 661-8000	Fax	(212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	FRANCOIS	Middle Initial		Family Name	DIETLIN	Suffix e.g. Jr.	
Inventor's Signature	Dietlin			Date	05/02/98		
Residence: City		State		Country	France	Citizenship	French
Post Office Address	5, rue du Canada -						
Post Office Address							
City	LE PECQ	State		Zip	F-78230	Country	France

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(c))--SMALL BUSINESS CONCERN

Docket Number (Optional): GEI-06

Applicant or Patentee: FREDJ Danièle
Serial or Patent No.: PCT/FR97/01452
Filed or Issued: August 5, 1997
Title: NOVEL STABLE...FOR PREPARING SAME

I hereby declare that I am

☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN SCR Pharmatop
ADDRESS OF SMALL BUSINESS CONCERN 5, rue d'Angiville, F-78000 Versailles France

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

☐ the specification filed herewith with title as listed above.
☒ the application identified above.
☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

☐ no such person, concern, or organization exists.
☒ each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING FREDJ Danièle

TITLE OF PERSON IF OTHER THAN OWNER

ADDRESS OF PERSON SIGNING 13bis, chemin des Rougemonts - F-91190 GIF-SUR-YVETTE (FR)

SIGNATURE Danièle Fredj DATE 04/20/1998